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The following are my comments on the Draft "Guidance for Industry ANDA's: Impurities in Drug Products"

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The draft guidance represents a step in the right direction and establishes a policy from CDER that all drug products should have established levels of impurities. However, the major overall deficiency in this document is that it is written from an academic and FDA reviewers perspective, and fails to address compliance and enforcement issues that face the Industry, and particularly the Generic Industry.

Historically, a major issue associated with enforcement of the FD&C Act has been the reliance of FDA Field Laboratories analyzing samples to determine compliance with established specifications. Classically, drug product specifications, particularly for generic drug products from different manufacturers have been the same. This has enabled the FDA and other Government Agencies to survey the Industry and evaluate compliance among different manufacturers of the same products. Thus, there has been the reliance of one set of specifications and one referee test method to assure compliance. This is probably why the USP is recognized in the FD&C Act as a resource for setting standards, particularly for marketed and generic products. To have different levels of impurities, different specifications, different methods of testing for each specific generic manufacturer of drug product would present an enforcement nightmare. For example, how would the FDA ever be able to support taking regulatory action against one manufacturer, who complies with a looser specification of a competitor, but not with their established filed specification? Process capability is not a concept that can or should be applied to the Generic Industry for the establishment of official specifications.

The concept of classifying impurities as degradants only, and not including impurities from the synthesis process also contradicts the classic FDA enforcement philosophy (refer to lines 5-7). Typically, an FDA or other Government or enforcement agency would collect a sample of a manufacturer's product and analyze it against a specification and test it by a filed or published (USP) method. Since the USP and FDA established many years ago that excipients may not interfere with official methods, any impurity would be counted in the total impurity specification. It would be extremely difficult for a Regulatory Compliance Manager to determine if an impurity is a synthesis impurity or a degradant. It is recognized that in an academic or international atmosphere, where enforcement is not an issue, it may be acceptable to discount synthesis impurities. However, in an enforcement arena, and particularly when generic products are concerned, total impurity specifications need to include all impurities.

Typically, in a FDA Inspection, the FDA Investigator and/or chemist will review chromatograms and add up all impurities to determine compliance with a specification. Since many drug substance impurity methods differ from the drug product method, it would be extremely difficult for the dosage form manufacturer to discount chromatographic peaks as being synthesis impurities.

The document may also be sending the wrong signal to the generic industry when dealing with the identification of impurities below the threshold level of .1% (lines 76-80). There should be some type of statement that while low level impurities do not need to be identified, they need to be included in the determination of compliance with the total impurity specification. Table 2 (lines 331-334) for reporting of degradants needs to either be eliminated or modified. In reality, thresholds for counting (reporting) impurities is less than .1% for products with a daily dose of less than 1Gm.

There is also a major inconsistency on page 8 (lines 225-234) that points out that the level of degradant can be established for the generic product which is up to 2 times the level found in the innovator product (RLD). If the innovator level of impurity is close to its specification, a generic product could have an impurity level of almost double the innovator specification. Again, from an enforcement perspective, how can the FDA support a regulatory action against an innovator company which has a specification tighter than the specification established by a generic manufacturer.

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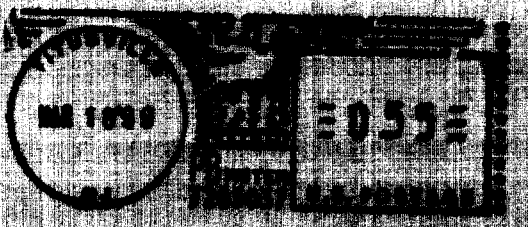

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